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(54) **Title:** ULTRASONIC TRANSDUCING PROBE WITH LIQUID FLOW-THROUGH CAPABILITY AND RELATED AUTOMATED WORKSTATION AND METHODS OF USING SAME

(57) **Abstract:** A hollow probe cooperates with an ultrasonic transducing device designed with liquid flow-through capability. The probe and transducing device are combined into a probe assembly, which can be integrated into an automated liquid handling workstation. As a functional component of the workstation, the probe can be connected to and manipulated by a robotic arm of the workstation, and thus programmed to move in three-dimensional space to and from various locations of the sampling apparatus. In particular, the probe can be inserted into the individual wells or test tubes of a plate or rack utilized to contain sample substances. The probe can be used to conduct a variety of liquid handling tasks and additionally can be used to ultrasonically excite sample substances contained in the individual wells of the plate, thereby improving dilution of such sample substances and increasing throughput of any given sample preparation procedure. A liquid level detection device can be connected to the probe assembly.

Description

ULTRASONIC TRANSDUCING PROBE WITH LIQUID FLOW-THROUGH CAPABILITY AND RELATED AUTOMATED WORKSTATION AND METHODS OF USING SAME

Technical Field

The present invention generally relates to an ultrasonic probe adapted for use with an automated workstation, and methods for using the probe in liquid handling and analytical processes. In particular, the present invention relates to an ultrasonic probe having liquid flow-through properties which is adapted to cooperate with a programmable robotic arm.

Background Art

As part of many compound generation and screening processes, small quantities of compound, in the form of powder or particles, are often deposited onto the well surfaces of plates such as microtitre and deep-well plates. Modern processes usually require the use of 96-well plates and are carried out in an automated manner at a workstation having robotic liquid-handling capabilities. The deposited solids often must be dissolved in preparation of a further task such as liquid chromatography analysis. In a time-consuming process, exact portions of solvent are added to each well of a microtitre plate. Each plate is then sealed to prevent evaporation, although it has been observed by those skilled in the art that evaporation is still a problem which can reduce the accuracy of analytical results. In order to successfully implement a high-throughput screening process, the researcher may prepare as many as fifty plates at a time. To ensure that the solids deposited in the well are completely dissolved, it is often required that the entire microtitre plate be ultrasonically excited for a period of time after the addition of solvent. Unfortunately, this process of gross or bulk sonication of the entire plate requires a large power output and tends to raise the temperature of both the plate and its contents. As a result, gross sonication bears an unacceptable risk that the

compounds become damaged or chemically altered to a degree such that the compounds are rendered useless or the ensuing analytical tasks become unverifiable or inaccurate. Also, the power delivered to each individual well may differ when the bulk sonication approach is employed, resulting in non-uniform heating of the samples. Moreover, the ratio of solvent to compound must be kept high to prevent precipitation, which can lead to less accurate analytical results.

Another approach toward ensuring complete dissolution has been to manually agitate the plate. The disadvantages of this approach, including the time, imprecision and human effort required, are readily acknowledged by those skilled in the art.

Accordingly, those skilled in the art will appreciate the need for an apparatus which reduces the amount of time required to dissolve solid-phase compound samples in wells, reduces the amount of solvent evaporation, permits a higher concentration of compound within wells, enables sonic excitation to be effected in the individual wells of a plate, enables sonication to be performed at a lower power level, and enables individual analyte samples to be aspirated immediately after dissolution. Such an apparatus would advantageously result in relatively little sample temperature rise, increased automation of the screening or liquid handling process, elimination of compound damage, and would therefore yield a more accurate and repeatable analysis. The present invention, as described hereinafter in the context of exemplary embodiments and processes, is provided to meet these needs.

Disclosure of the Invention

The present invention generally provides a hollow probe which cooperates with an ultrasonic transducing device designed with liquid flow-through capability. The probe and transducing device are combined into a probe assembly which is advantageously adapted to be integrated into an automated liquid handling or sampling apparatus or workstation. As a functional component of the workstation, the probe can be connected to and manipulated by a robotic arm of the workstation, and thus programmed to move in three-dimensional space to and from various

locations of the sampling apparatus. In particular, the probe can be inserted into the individual wells or test tubes of a plate or rack utilized to contain sample substances. By the design of the present invention, the probe can be used to conduct a variety of liquid handling tasks and additionally can be used to ultrasonically excite sample substances contained in the individual wells of the plate, thereby improving dilution of such sample substances and increasing throughput of any given sample preparation procedure.

According to one aspect of the present invention, an apparatus is provided for use as part of a fluid handling system and is adapted for selectively ultrasonically exciting drug, compound or chemical containing samples provided in the form of liquids, suspensions, wetted compounds, solutions or emulsions. The apparatus comprises a movable robotic assembly and an ultrasonic transducer probe assembly attached to the robotic assembly. The probe assembly includes an ultrasonic transducer body defining an internal fluid conduit and an elongate hollow probe member defining an internal bore. The probe member is disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member. The internal bore of the probe member fluidly communicates with the internal conduit of the transducer body, and terminates at an orifice defined by the probe member.

According to another aspect of the present invention, the probe assembly includes a housing attached to the robotic assembly, and the transducer body is disposed in the housing.

According to an additional aspect of the present invention, the probe member has a sharpened tip adapted to puncture a closure provided with a substance container.

According to a further aspect of the present invention, an apparatus has liquid flow-through capability and is adapted to sonicate a drug, compound or chemical containing substance, and is further adapted to detect the level of the substance in a container. The apparatus comprises an ultrasonic transducer probe assembly and a liquid level detection device electrically connected to the probe assembly. The ultrasonic transducer probe assembly includes an ultrasonic transducer body

defining an internal fluid conduit and an elongate hollow probe member defining an internal bore. The probe member is disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member. The internal bore fluidly communicates with the internal conduit and terminates at an orifice defined by the probe member.

According to yet another aspect of the present invention, a fluid handling workstation is provided, and is adapted to perform sonication tasks in individual wells of well-containing plates. The workstation comprises a workstation frame including a lateral track; a robotic assembly movable along the lateral track; and an ultrasonic transducer probe assembly attached to the robotic assembly. The probe assembly includes an ultrasonic transducer body defining an internal fluid conduit and an elongate hollow probe member defining an internal bore. The probe member is disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member. The internal bore of the probe member fluidly communicates with the internal conduit of the transducer body, and terminates at an orifice defined by the probe member.

According to still another aspect of the present invention, the robotic assembly includes a vertical arm defining a vertical track and a horizontal arm defining a horizontal track. The probe assembly engages the vertical arm and is movable along the vertical track, the vertical arm engages the horizontal arm and is movable along the horizontal track, and the horizontal arm is movable along the lateral track of the workstation frame.

According to a further aspect of the present invention, the workstation comprises an injection port accessible by the probe member. The injection port includes an annular sealing member adapted to receive the probe member therethrough and an injection bore adapted to receive the probe member therein. The sealing member is disposed in an internal sealing region defined by the injection port.

According to a still further aspect of the present invention, the workstation comprises a rinse station accessible by the probe member. The rinse station

includes a main body and an adapter fitting attached to the main body. The main body defines a rinsing bore adapted to receive the probe member therein. The adapter fitting has an aperture fluidly communicating with the rinsing bore and is adapted to receive the probe member therethrough. The aperture is sized to ensure that the probe member does not contact the main body when inserted into the rinsing bore.

The probe assembly and/or workstation provided in accordance with the present invention can operate in conjunction with a number of other devices or instruments employed in liquid handling and sample preparation tasks. Such devices and instruments include, without limitation, a dilution device, a syringe pump, chromatography apparatus, and the like.

The present invention also provides a process for preparing drug, compound or chemical containing fluid samples for subsequent analysis. An automated support assembly and an ultrasonic transducer probe assembly are provided. The ultrasonic transducer probe assembly is attached to the support assembly, and includes an ultrasonic transducer body defining an internal fluid conduit and an elongate hollow probe member defining an internal bore. The probe member is disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member. The internal bore fluidly communicates with the internal conduit and terminates at an orifice defined at a tip of the probe member. A plate including a plurality of wells is provided. One or more of the wells contain a drug, compound or chemical substance. The support assembly transports the probe assembly to the plate and lowers the probe member into a selected one of the wells of the plate. The sample substance is at least partially diluted by causing a volume of solvent to flow through the internal fluid conduit of the ultrasonic transducer body of the probe assembly, through the internal bore of the probe member, out from the orifice of the probe member, and into the selected well of the plate. The sample substance is diluted by activating the probe assembly to transfer vibratory energy to the sample substance from the tip of the probe member. The addition of solvent and sonication of sample substance can be repeated for each well of the plate, and well as for any other

plates provided. Moreover, a quantity of sonicated sample substance can be withdrawn from the well into the probe member, so that this quantity can be transported to another location such as an injection port, a rinse station, or another plate.

The present invention also provides a sonicated sample substance prepared in accordance with the above-disclosed process.

The present invention further provides a sonicated organic tissue sample prepared in accordance with the above-disclosed process.

It is therefore an object of the present invention to provide an ultrasonic transducer device in which a probe can transmit vibratory energy to a substance to improve dissolution thereof, as well as aspirate and dispense the substance.

It is also an object of the present invention to provide an ultrasonic transducer device adapted to transport solvent to a sample substance, especially a substance contained in a well of a plate, sonicate the substance, and then immediately aspirate the substance from the well if desired.

It is another object of the present invention to provide an automated liquid handling workstation which includes the novel ultrasonic transducer device instead of a more conventional sampling needle.

It is yet another object of the present invention to provide a rinse station for a liquid handling apparatus which is adapted to receive the novel ultrasonic transducer device.

It is still another object of the present invention to provide an injection port, especially of the type employed in conjunction with chromatography equipment, which is adapted to receive the novel ultrasonic transducer device.

It is a further object of the present invention to provide a process for preparing sample substances using the novel ultrasonic transducer device.

Some of the objects of the invention having been stated hereinabove, other objects will become evident as the description proceeds, when taken in connection with the accompanying drawings as best described hereinbelow.

Brief Description of the Drawings

Figure 1 is a perspective view of an automated liquid handling apparatus in which an ultrasonic transducing probe and related components have been integrated in accordance with the present invention;

Figure 2 is another perspective view of the liquid handling apparatus illustrated in Figure 1 wherein the plates have been removed for clarity of description;

Figure 3 is a perspective view of an ultrasonic transducing probe assembly mounted to a robotic arm of the liquid handling apparatus illustrated in Figure 1;

Figure 4 is a perspective, partially cutaway view of an adapter housing in which an ultrasonic transducing probe is mounted in accordance with the present invention;

Figure 5 is an exploded view of the ultrasonic transducing probe assembly illustrated in Figure 3;

Figure 6 is a cutaway view of the ultrasonic transducing probe provided in accordance with the present invention;

Figure 6A is a cutaway view of an alternative ultrasonic transducing probe provided in accordance with the present invention;

Figure 7 is a partially cutaway view of the ultrasonic transducing probe inserted into an injection port in accordance with the present invention;

Figure 8 is an exploded view of the ultrasonic transducing probe and injection port illustrated in Figure 7;

Figure 9 is an exploded, cutaway view of the injection port illustrated in Figure 7;

Figure 10 is a cutaway view of the ultrasonic transducing probe inserted into a rinse station port in accordance with the present invention; and

Figure 11 is a schematic view of the ultrasonic transducing probe operating in conjunction with a liquid level detection device in accordance with the present invention.

Detailed Description of the Invention

Referring now to Figures 1 and 2, an automated liquid handling or sampling apparatus, generally designated **10**, is illustrated in accordance with the present invention. In the exemplary, inventive embodiment illustrated herein, sampling apparatus **10** can be a modified version of a commercially available GILSON™ apparatus, of which various models are available from Gilson Medical Electronics, Inc. For example, a GILSON™ Model No. 215 platform has been found to be suitable in the practice of the present invention. Other apparatuses or platforms which could be adapted to operate in conjunction with the present invention include ZYMARK™ and PACKARD™ models. It will be understood, however, that automated sampling apparatus **10** provided in accordance with the present invention can be constructed from fully original components. Thus, the apparatus depicted in Figures 1 and 2 is intended herein to represent either a fully original embodiment or a commercially available platform modified or adapted in accordance with the present invention. Sampling apparatus **10** is generally used for sample preparation, and is capable of being programmed by means of written software to perform a wide variety of liquid handling and preparation tasks. For example, sampling apparatus **10** can be equipped with an electrical input/output interface (not shown) to enable communication with a suitable liquid or gas chromatography analysis device if desired.

Sampling apparatus **10** ordinarily includes a dilution module, generally designated **12**, which controls the movement of liquid within various points of sampling apparatus **10**. A valve **14** is mounted to dilution module **12**, and a syringe **16** depends therefrom. As is well known in the art, a movable boundary is disposed within syringe **16** and is actuated by a stepper motor and associated drive unit (not shown) to provide both aspiration and positive pressure to the various fluid conduits associated with sampling apparatus **10**. The actuation may be programmed into sampling apparatus **10**. A length of solvent inlet tubing **18**, preferably formed of PTFE, is connected to valve **14** to supply rinse solvent to sampling apparatus **10** from a solvent reservoir **20**. Examples of solvents commonly

used include methanol, ethanol, water, acetonitrile, acetone, isopropanol, hexane, diethyl ether, and toluene.

Sampling apparatus **10** generally includes a main frame **22**. A plate holder **24** is attached to main frame **22** and includes a series of adapter plates **26**. As shown in Figure 1, a plurality of plates **28** may be mounted on plate holder **24** by means of alignment with adapter plates **26**. A wide variety of plates **28**, such as microtitre plates, deep-well plates and test tube racks, are available depending on the desired application. Each plate **28** includes an array of wells for containing reagents, compounds, samples of liquid substances, and the like, or includes holes for holding vials, test tubes or other vessels of differing sizes for this purpose.

As best shown in Figure 2, also attached to main frame **22** is a movable robotic assembly, generally designated **40**. Robotic assembly **40** includes a horizontal arm **42** and a vertical arm **44**. Horizontal arm **42** is slidably carried on a track **46** mounted within main frame **22**. An additional track **48** is formed on horizontal arm **42**, in which vertical arm **44** is slidably carried. One or more stepper motors and associated drives (not shown) disposed within main frame **22**, or on vertical arm **44** as in the case of motor **50**, provide actuation for robotic assembly **40** along a three-axis coordinate system. As in the case of dilution module **12**, this actuation may be controlled by software interfacing with sampling apparatus **10**. In the conventional form of sampling apparatus **10**, a sampling needle (not shown) would be movably mounted to a vertically disposed track **49** of vertical arm **44** and employed to load and extract liquid substances to and from different positions over and proximate to plates **28** shown in Figure 1. A length of transfer tubing **54** (see Figure 1), preferably formed of PTFE, would provide fluid communication between this sampling needle and valve **14** of dilution module **12**. In the present invention, however, as shown in Figures **1** and 2, an ultrasonic transducing probe assembly, generally designated **80**, equipped with a probe **82** having liquid flow-through capability has been substituted in the place of a conventional sampling needle.

Through the movement of horizontal arm **42**, vertical arm **44** and ultrasonic probe assembly **80**, probe **82** according to the present invention may be programmed to accomplish not only sonication tasks, but also chromatography

injection, and a variety of liquid handling and sample preparation tasks such as transferring solvent to vials and/or wells disposed in plates **28** and transferring liquid substances from one vial or well to another vial or well. A remote keypad or computer **60** (see Figure 1) may be connected to sampling apparatus **10** via a ribbon cable **62** and used for entering instructions into memory, recalling previously written programs, and otherwise controlling the operation of sampling apparatus **10**, including robotic assembly **40** and ultrasonic probe assembly **80**.

Sampling apparatus **10** also includes an injection port, generally designated **120**, which is accessible by probe **82**. Injection port **120** fluidly communicates with an injection valve **122**, and is used to deliver samples to a high-pressure liquid chromatography (HPLC) device or gas chromatography device (not shown) if desired. Sampling apparatus **10** further includes a rinsing station, generally designated **140**, which may be used for eliminating waste products and purging the fluid paths of sampling apparatus **10** between the operative steps of an intended procedure. Rinsing station **140** includes a trough or a cup **142**, which is also accessible by probe **82**, and a drain tube **144** (see Figure 2).

Referring now to Figures 3 - 6, ultrasonic transducing probe assembly **80** is illustrated in more detail. Probe assembly **80** includes a ultrasonic converter body or handpiece **84**, such as a MISONIX™ handpiece commercially available from Misonix Inc. of Farmingdale, New York, as Part No. 2325. Converter body **84** has a flow-through design, and accordingly includes an internal passage (not shown) to enable fluid to flow from transfer tubing **54**, through a tubing adapter **86** and a top fitting **88**, through converter body **84**, and finally to probe **82**. A suitable probe **82** is also available from Misonix Inc. as Part No. 1825. As best shown in Figure 6, the body of probe includes a neck section **82A** to which top fitting **88** is secured such as by threading. The outside diameter of probe **82** is reduced over one or more tapered sections. The outside diameter of a distal section **82B** is small enough to permit probe **82** to be inserted into the wells of a standard-sized plate **28**. Probe **82** has a hollow interior bore **92** terminating at a distal orifice **94** defined at a tip **82C** of probe **82**. Hollow interior bore **92** includes a reduced-diameter section within distal section **82B** of probe **82**. In the exemplary embodiment, orifice **94** has a 0.6 mm

diameter. Probe **82** serves as an elongate horn member which transfers sonic energy to probe tip **82C**. In use, when a fluid such as a solvent is pumped through converter body **84** and probe **82** with probe assembly **80** activated, a fine mist can be produced at orifice **82C**. In the present embodiment, probe assembly **80** has been designed so as not to leak under operating back pressures of up to approximately 120 psi, which makes probe assembly **80** suitable for use in conjunction with liquid chromatographic injection.

An alternative version of probe **82** is illustrated in Figure 6A. Probe tip **82C** in Figure 6A has been cut, either arcuately or at an angle such as 30E, so as to present a sharpened edge. The sharpened edge is useful in the case where a substance container such as a vial or test tube includes a closure such as a septum. The sharpened edge facilitates the penetration or puncturing of the septum by probe **82**.

Referring back to Figures 3 - 5, converter body **84** fits into a probe assembly adapter or housing **102** and is protected by a removable front cover **104**. Probe assembly adapter or housing **102** is preferably constructed from machined aluminum, and is shaped to accommodate converter body **84** as well as tubing adapter **86** and fitting **88**. For example, an elongate chamber **102A** can be formed to accommodate converter body **84**, and an upper chamber **102B** formed to accommodate tubing adapter **86** and fitting **88**. In addition, a slot **102C** is formed on probe assembly adapter **102** to accommodate fluid transfer tubing **54** (see Figure 1) and an electrical control cable **104** to pass therethrough. Control cable **104** is attached between converter body **84** and a remote generator device or base station **106** so that base station **106** (see Figure 1) can provide electrical power to converter body **84** and thus drive the vibratory action. Another cable (not shown) can be run between base station **106** and computer **60** or other electronic device (see Figure 1) to turn probe assembly **80** ON and OFF. Converter body **84** can be secured within probe assembly adapter **102** such as by threading a screw (not shown) into an aperture **102D** of probe assembly adapter **102**. As shown in Figure 3, probe assembly adapter **102** is adapted to fit onto vertical arm **44** of robotic assembly **40** in the place of a standard sampling needle, using the same mounting boss and

screws **108**. Preferably, the respective lengths of probe assembly adapter **102** and probe **82** are such that probe tip **82C** matches the position originally assumed by the sampling needle, and hence eliminates the need for major z-axis compensation.

Referring to Figures 7 - 9, injection port **120** is illustrated in more detail. Injection port **120** is designed to receive probe **82** and enable probe **82** to inject sample media without leakage. Injection port **120** includes an upper body **124**, a lower body **126**, a collar **128**, and a TEFLON7 seal **130**. Upper and lower bodies **124** and **126** may be secured together by providing mating threads on upper and lower bodies **124** and **126** and on collar **128**. Upper body **124** has a tapering inside surface **124A** (see Figure 9) to accommodate probe **82**. Lower body **126** includes an internal flow-through bore **126A** with which tip **82C** of probe **82** makes contact. As shown in Figure 7, tip **82C** and internal bore **126A** preferably have complementary tapered or chamfered surfaces to improve their contact. An internal volume **126B** of lower body **126** defines a sealing region into which seal **130** is installed. Seal **130** is generally interposed between upper and lower bodies **124** and **126** in coaxial relation to distal section **82B** of probe **82**, thereby filling the space of the sealing region and establishing a good seal between probe **82** and injection port **120**.

Referring now to Figure 10, rinsing station **140** is illustrated in more detail. Rinsing station **140** includes a main body **146** and an annular adapter fitting **148** attached to main body **146** generally above cup **142**. Main body **146** includes a rinsing bore **152** having an open end **152A** communicating with an aperture **148A** of fitting **148** and a closed end **152B** terminating at a point within main body **146**. Rinsing bore **152** may be tapered to accommodate probe **82**. The diameter of aperture **148A** is sized relative to rinsing bore **152** such that when probe **82** is inserted through aperture **148A** into rinsing bore **152**, the outer surfaces of probe **82** are close to but not touching rinsing bore **152**. Rinsing station **140** is thus designed to receive probe **82** therein so that cleaning solvent can be aspirated through probe **82** and its orifice **94**, and conducted through rinsing bore **152** so that both the inner and outer surfaces of probe **82** are contacted by the cleaning solvent and cleaned thereby.

An exemplary operation of probe **82** as integrated into sampling apparatus **10** will now be described, with general reference being made to all Figures disclosed herein. Plates **28** such as microtitre plates containing samples of dry compound in one or more wells (or, alternately, racks supporting a plurality of test tubes, vials or other substance containers) are placed into plate holder **24**. Depending on the particular application, the respective labels or identifications of the compounds, their coordinate positions in 96-well plate **28**, their respective masses, and the positions of plates **28** in plate holder **24** can be inputted into computer **60** as part of the programming of tasks to be performed by robotic assembly **40** and dilution module **12**. Also, it may be desired to initially cause robotic assembly **40** to transport probe assembly **80** to rinse station **140** and insert probe **82** therein, and to cause dilution module **12** to draw a volume of rinse solvent from reservoir **20** and pump the solvent through probe **82** in order to flush the fluid lines and pre-clean probe **82**. Upon activation of sampling apparatus **10**, robotic assembly **40** transports probe assembly **80** to the wells of one or more plates **28**, lowers probe **82** into individual wells, and dispenses a controlled amount of solvent or other fluid through probe **82** into each well. If desired, sampling apparatus **10** may be programmed to mix two or more different types of solvents in a given well in order to create binary, tertiary, quaternary, etc. solvent systems. If a closure such as a septum exists, probe **82** is capable of puncturing such a barrier.

Prior to sonication, residual solvent can be removed from probe **82** by drawing air in order to prevent excessive or unwanted dilution of a sample. At each well, probe **82** is then caused to make contact with the wetted substance contained therein, and probe assembly **80** is activated to transfer vibrational energy to tip **94** of probe **82** and thereby sonicate the substance for a predetermined period of time (e.g., a few seconds). The primary function of the sonication process in the exemplary embodiment is to effect complete dissolution of the dry compound contained in a given well. However, in the appropriate situation, vibrating probe **82** could be operated long enough to deliberately cause a rise in sample temperature.

After sonication, probe **82** is further employed to aspirate a predetermined quantity of sample of the dissolved compound. Robotic assembly **40** can then

transport probe assembly **80** to a variety of locations of sampling apparatus **10**, depending on the particular procedure being undertaken. For instance, probe assembly **80** can move to another plate **28** containing wells or holding test tubes, and the aspirated sample can be dispensed through probe tip **94** into the wells or test tubes as part of some analytical or combinatorial process. In addition, probe assembly **80** can move to injection port **120** and probe **82** inserted therein as shown in Figure 7, and the aspirated sample can then be provided for analysis in a liquid chromatograph, for example. It is possible to provide more than one chromatograph, such that multiple analyses can occur simultaneously to thereby increase throughput. It is also possible to provide a port or other probe receiving means which fluidly connects probe to a gas chromatograph. Finally, probe assembly **80** can be moved to rinse station **140** and probe **82** installed therein as shown in Figure 10, so that probe **82** can be cleaned to prevent cross-contamination.

Sampling apparatus **10** can be programmed to execute one or more of the above-described process steps for each well of one or more plates **28** in a repeatable, cyclical process.

As an additional application of the present invention, plates **28** could be constructed from a translucent or transparent material such as quartz, to enable the examination of optical and spectral properties of the substances residing in each well. Sample substances could be initially provided in a quartz microtitre plate, or probe assembly **80** could be employed to transport samples to the quartz plate from another type of plate.

In another, more specific application of the present invention, tissue samples can be homogenized in preparation for RNA extraction. In this application, tissue samples are added to the wells of plate **28** or to individual containers such as EPPENDORFJ tubes held in a suitable plate **28**. In the latter case, plate **28** is provided in the form of a rack adapted to hold such tubes. After the addition of a suitable solvent to a given tissue sample, the sonication carried out by probe **82** generally occurs over a period longer than a few seconds, for example approximately 30 to 60 seconds, in order to adequately break up and dissolve the

tissue sample. Probe **82** is then used to aspirate and deliver a predetermined quantity of the dissolved tissue sample to another container for further processing. This other container may be mounted at sampling apparatus **10**.

Referring now to Figure 11, a liquid level detection task can be made a part of the various processes involving the use of probe **82**. A liquid level detection device **200**, such as a conventional capacitive-type transducer, is electrically coupled to probe assembly **80** such as at converter body **84**. Liquid level detection device **200** is also connected to some type of readout or display **204**, which may be part of an electronic device separate from or integrated into sampling apparatus **10** of Figures 1 and 2. When probe **82** is inserted into a well or other container, represented in Figure 11 as **206**, and contacts the solution or suspension contained therein, device **200** can measure the level of liquid in container **206**. An ON/OFF switch **208** can be provided on control cable **104** to isolate the operation of liquid level detection device **200** and thereby ensure its accuracy. Liquid level detection device **200** correlates the level of solution or suspension in container **206** to a sensed measurement of capacitance, and readout **204** displays an indication of that level.

It will be understood that various details of the invention may be changed without departing from the scope of the invention. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation—the invention being defined by the claims.

CLAIMS

What is claimed is:

1. An apparatus adapted for use as part of a fluid handling system and adapted for selectively ultrasonically exciting drug, compound or chemical containing samples provided in the form of liquids, suspensions, wetted compounds, solutions or emulsions, the apparatus comprising:
   (a) a movable robotic assembly; and
   (b) an ultrasonic transducer probe assembly attached to the robotic assembly, the probe assembly including an ultrasonic transducer body defining an internal fluid conduit and an elongate hollow probe member defining an internal bore, the probe member disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member, the internal bore fluidly communicating with the internal conduit and terminating at an orifice defined by the probe member.

2. The apparatus according to claim 1 wherein the robotic assembly includes a vertical arm defining a vertical track and a horizontal arm defining a horizontal track, and the probe assembly engages the vertical arm and is movable along the vertical track, the vertical arm engages the horizontal arm and is movable along the horizontal track, and the horizontal arm is movable along a lateral direction.

3. The apparatus according to claim 1 wherein the probe assembly includes a housing attached to the robotic assembly, and the transducer body is disposed in the housing.

4. The apparatus according to claim 1 wherein the transducer body is disposed in electrical communication with a power source.

5. The apparatus according to claim 1 wherein the internal fluid conduit of the transducer body fluidly communicates with a reservoir over a fluid transfer line.

6. The apparatus according to claim 1 wherein the internal fluid conduit of the transducer body fluidly communicates with a fluid aspirating and pumping unit over a fluid transfer line.

7. The apparatus according to claim 6 wherein the fluid aspirating and pumping unit is part of a dilution device.

8. The apparatus according to claim 6 wherein the fluid aspirating and pumping unit includes a syringe-type pump.

9. The apparatus according to claim 6 wherein the fluid aspirating and pumping unit communicates with a reservoir over a fluid supply line.

10. The apparatus according to claim 1 wherein the probe member terminates at an acute probe tip adapted to penetrate a closure.

11. An apparatus having liquid flow-through capability and adapted to sonicate a drug, compound or chemical containing substance and to detect the level of the substance in a container, the apparatus comprising:
    (a) an ultrasonic transducer probe assembly including an ultrasonic transducer body defining an internal fluid conduit and an elongate hollow probe member defining an internal bore, the probe member disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member, the internal bore fluidly communicating with the internal conduit and terminating at an orifice defined by the probe member; and

(b) a liquid level detection device electrically connected to the probe assembly.

12. The apparatus according to claim 11 comprising a movable robotic assembly, wherein the ultrasonic transducer probe assembly is attached to the robotic assembly.

13. A fluid handling workstation adapted to perform sonication tasks in individual wells of well-containing plates, the workstation comprising:
    (a) a workstation frame including a lateral track;
    (b) a robotic assembly movable along the lateral track; and
    (c) an ultrasonic transducer probe assembly attached to the robotic assembly, the probe assembly including an ultrasonic transducer body defining an internal fluid conduit and an elongate hollow probe member defining an internal bore, the probe member disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member, the internal bore fluidly communicating with the internal conduit and terminating at an orifice defined by the probe member.

14. The workstation according to claim 13 wherein the robotic assembly includes a vertical arm defining a vertical track and a horizontal arm defining a horizontal track, and the probe assembly engages the vertical arm and is movable along the vertical track, the vertical arm engages the horizontal arm and is movable along the horizontal track, and the horizontal arm is movable along the lateral track of the workstation frame.

15. The workstation according to claim 13 wherein the probe assembly includes a housing attached to the robotic assembly, and the transducer body is disposed in the housing.

16. The workstation according to claim 13 comprising a plate removably mounted at the workstation and including an array of wells accessible by the probe member.

17. The workstation according to claim 13 comprising an injection port accessible by the probe member, the injection port including an annular sealing member adapted to receive the probe member therethrough and an injection bore adapted to receive the probe member therein, the sealing member disposed in an internal sealing region defined by the injection port.

18. The workstation according to claim 13 comprising a rinse station accessible by the probe member, the rinse station including a main body and an adapter fitting attached to the main body, the main body defining a rinsing bore adapted to receive the probe member therein, the adapter fitting having an aperture fluidly communicating with the rinsing bore and adapted to receive the probe member therethrough, the aperture sized to ensure that the probe member does not contact the main body when inserted into the rinsing bore.

19. The workstation according to claim 13 comprising a liquid level detection device electrically connected to the probe assembly

20. The workstation according to claim 13 wherein the probe member terminates at an acute probe tip adapted to penetrate a closure.

21. A process for preparing drug, compound or chemical containing fluid samples for subsequent analysis comprising the steps of:
(a) providing an automated support assembly;
(b) providing an ultrasonic transducer probe assembly attached to the support assembly, wherein the probe assembly includes an ultrasonic transducer body defining an internal fluid conduit and an elongate

hollow probe member defining an internal bore, the probe member is disposed in mechanical communication with the transducer body to enable vibratory energy to be transferred from the transducer body to the probe member, the internal bore fluidly communicating with the internal conduit and terminating at an orifice defined at a tip of the probe member;

(c) providing a plate including a plurality of containers, wherein at least some of the containers contain a drug, compound or chemical substance;

(d) causing the support assembly to transport the probe assembly to the plate and to lower the probe member into a selected one of the containers of the plate;

(e) at least partially diluting the sample substance by causing a volume of solvent to flow through the internal fluid conduit of the ultrasonic transducer body of the probe assembly, through the internal bore of the probe member, out from the orifice of the probe member, and into the selected container of the plate;

(f) sonicating the at least partially diluted sample substance by activating the probe assembly to transfer vibratory energy to the sample substance from the tip of the probe member; and

(g) repeating steps (d) through (f) at other containers of the plate.

22. The process according to claim 21 comprising the step of withdrawing a quantity of the sonicated sample substance from the selected container into the internal bore of the probe member.

23. The process according to claim 22 comprising the steps of causing the support assembly to transport the probe assembly to an additional plate and dispensing the withdrawn quantity of sonicated sample substance through the orifice of the probe member to a location of the additional plate.

24. The process according to claim 22 comprising the steps of providing an injection port including an injection bore and an annular sealing member disposed in an internal sealing region defined by the injection port, causing the support assembly to transport the probe assembly to the injection port, lowering the probe member into the injection bore and into the sealing member, and dispensing the withdrawn quantity of sonicated sample substance into the injection bore.

25. The process according to claim 21 comprising the steps of providing a rinse station including a main body defining a rinsing bore and an adapter fitting attached to the main body, the adapter fitting defining an aperture fluidly communicating with the rinsing bore, causing the support assembly to transport the probe assembly to the rinse station, lowering the probe member through the aperture of the adapter fitting and into the injection bore such that the probe member is spaced from the main body, and causing a rinse solvent to flow through the probe member into the rinsing bore, whereby inner and outer surfaces of the probe member are cleaned by the rinse solvent.

26. The process according to claim 21 comprising the step of providing a liquid handling apparatus to which the automated support assembly is movably mounted.

27. The process according to claim 21 comprising the step of using the probe member to puncture a closure of the selected container.

28. The process according to claim 21 comprising the step of using a liquid level detection device connected to the probe assembly to measure a level of the sample substance contained in the selected container.

29. A sonicated sample substance prepared according to the process of claim 21.

30. The process according to claim 21 wherein the sample substance is provided in the form of an organic tissue sample.

31. A sonicated organic tissue sample prepared according to the process of claim 30.

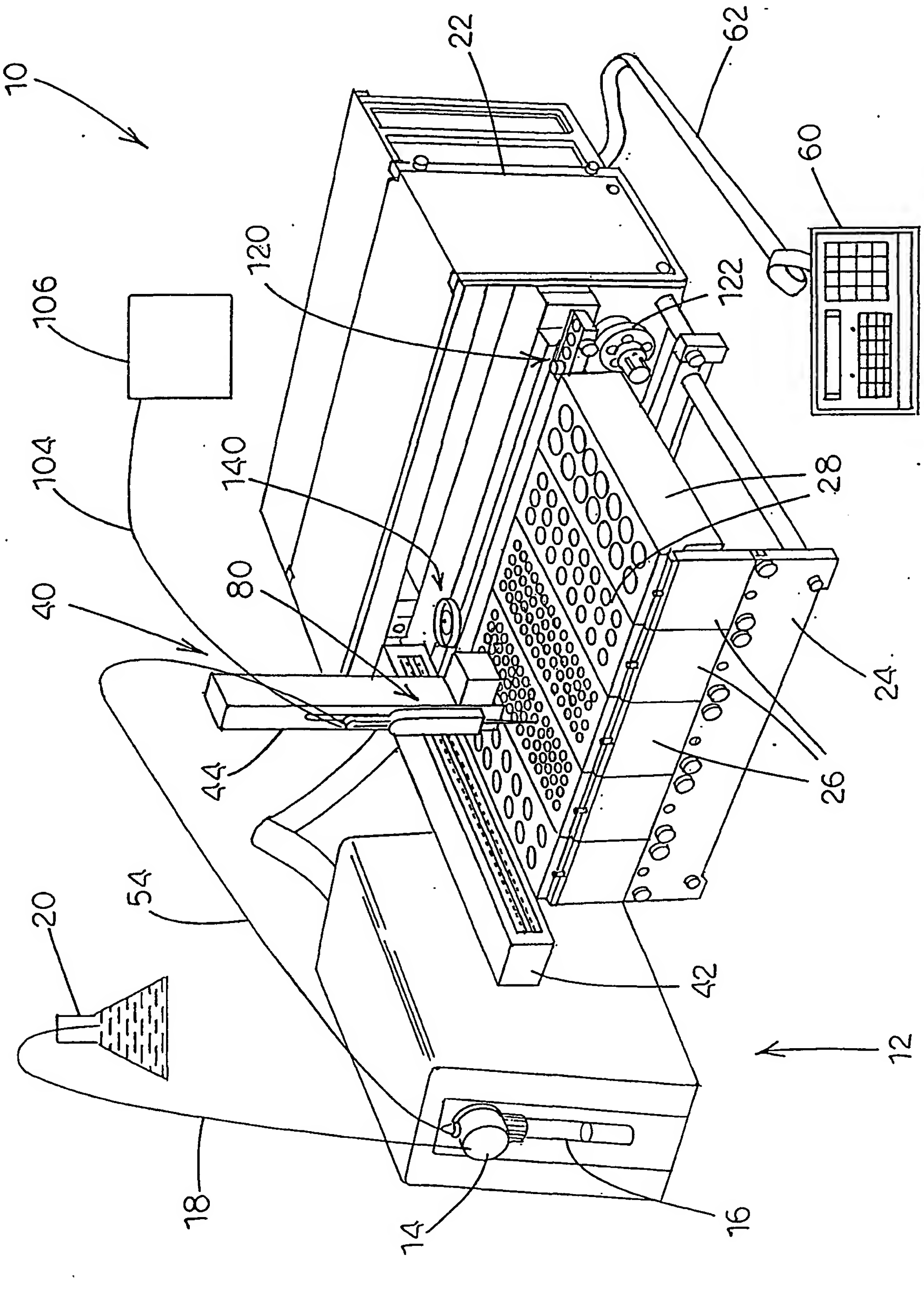
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FIG. 1

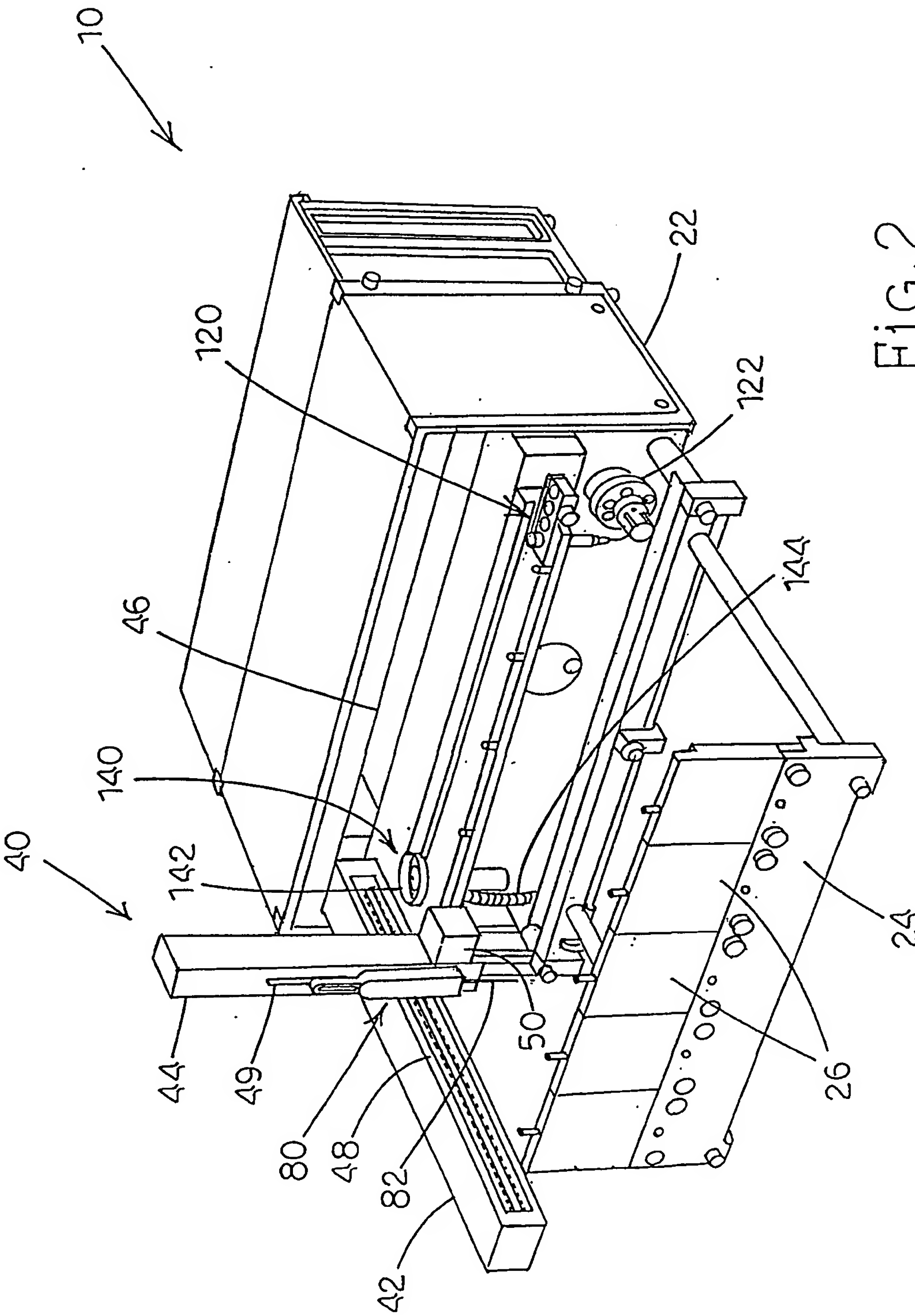

FIG. 2

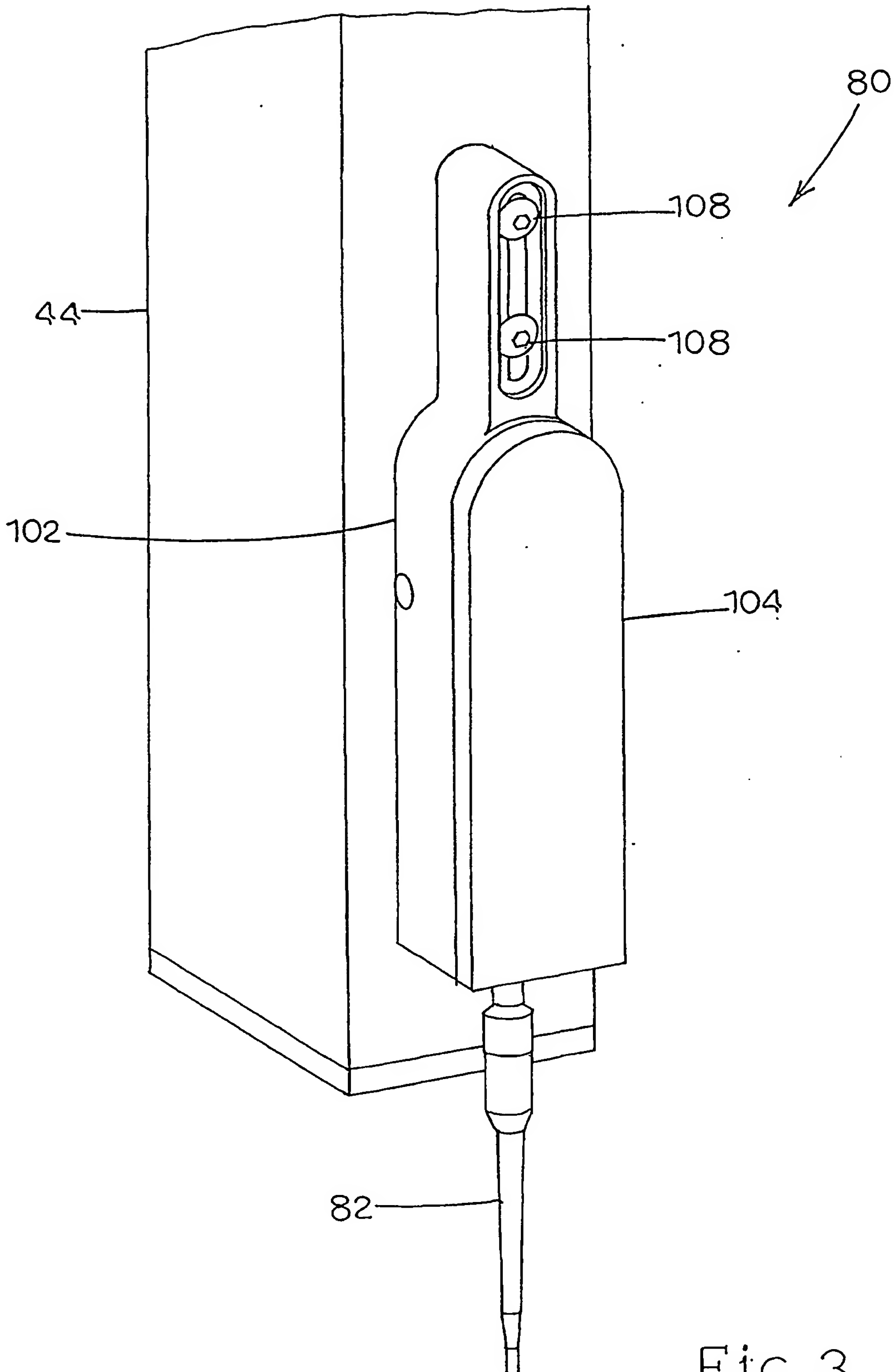

Fig.3

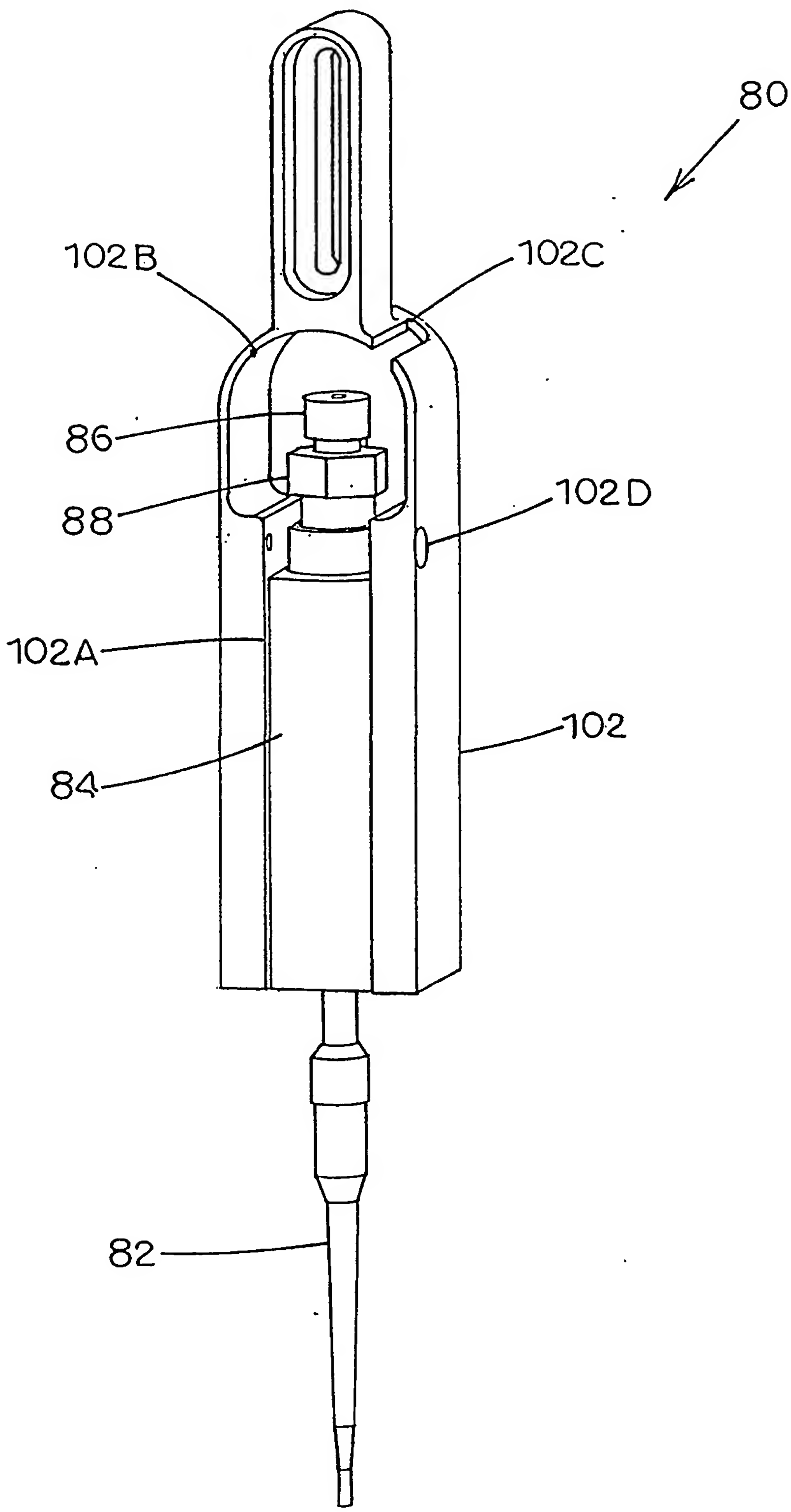

Fig 4

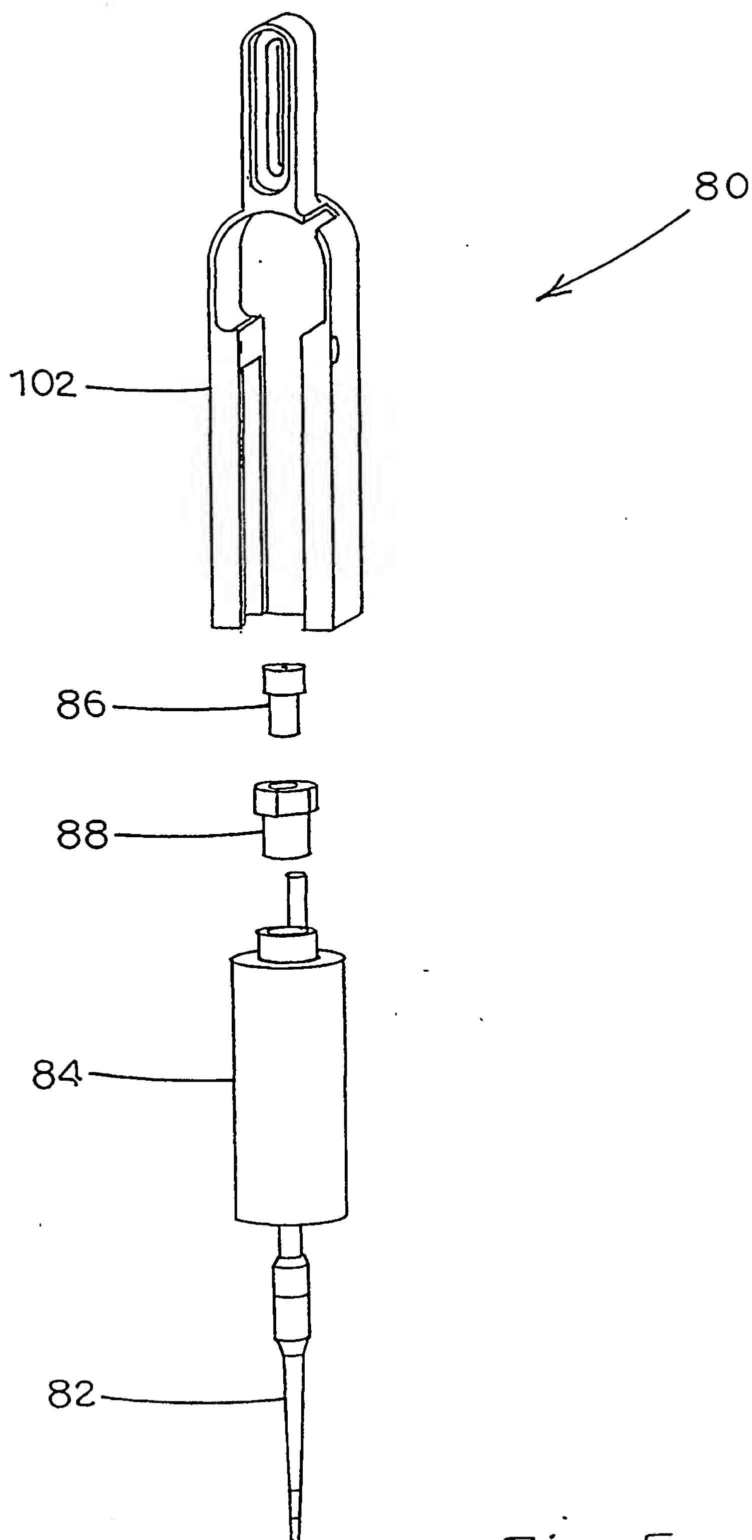

Fig.5

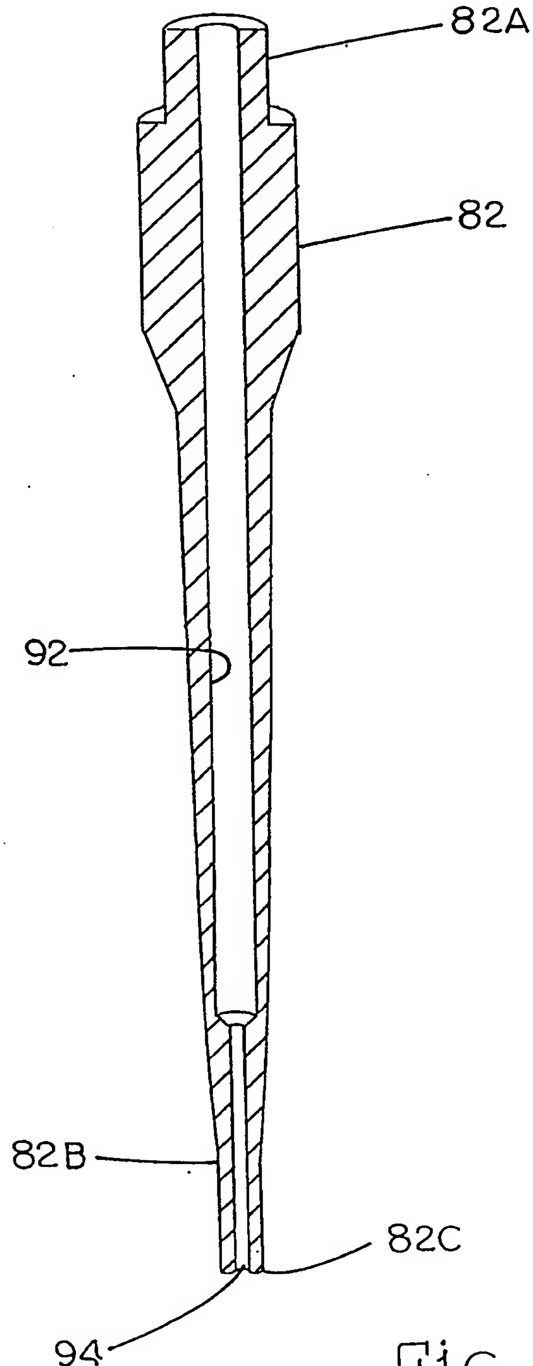

FIG. 6

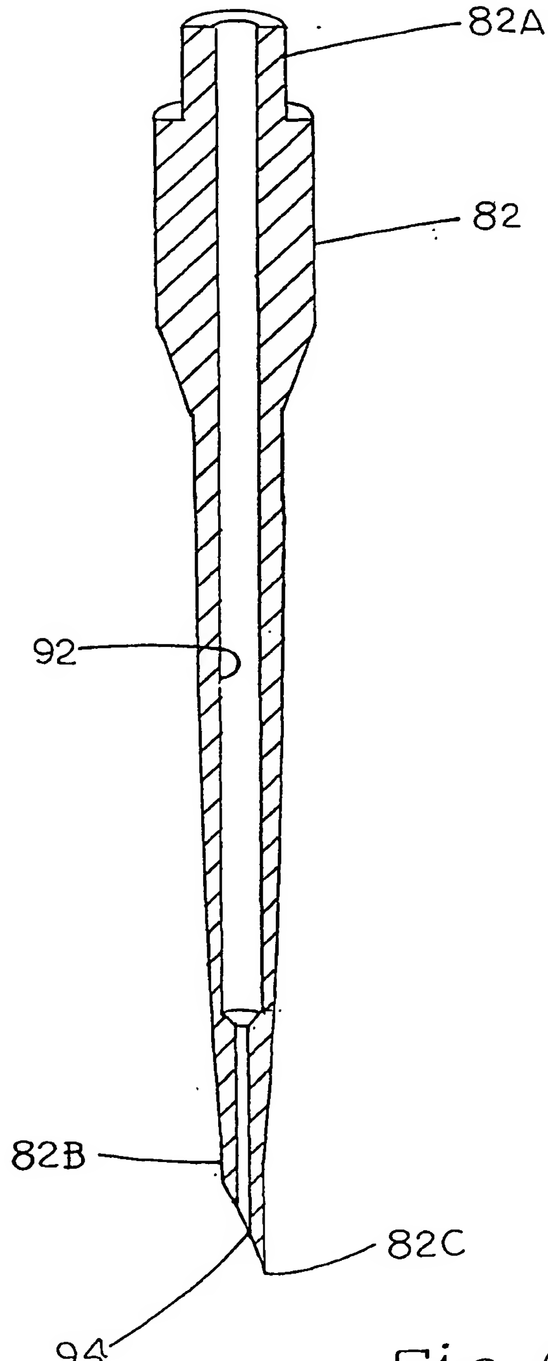

Fig.6A

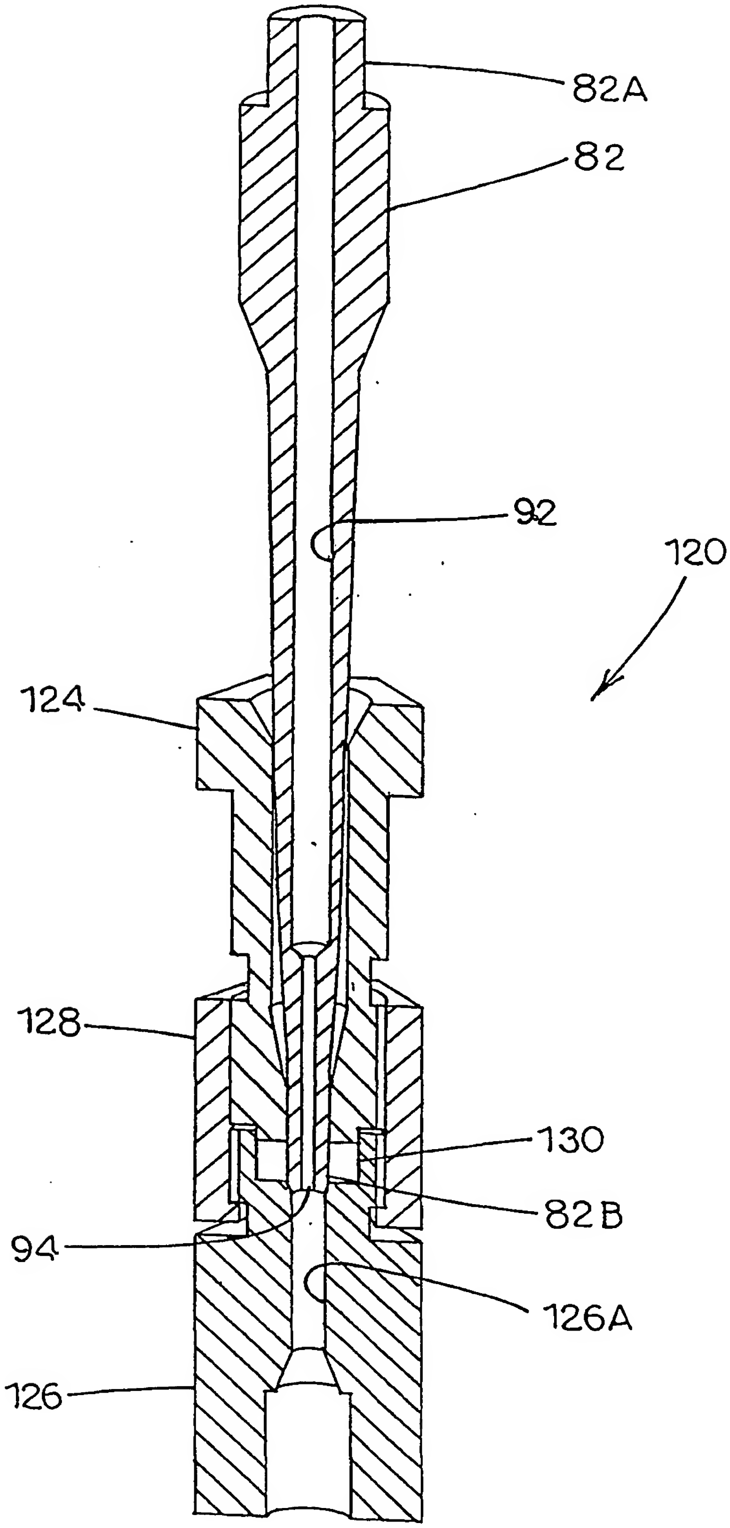

Fig.7

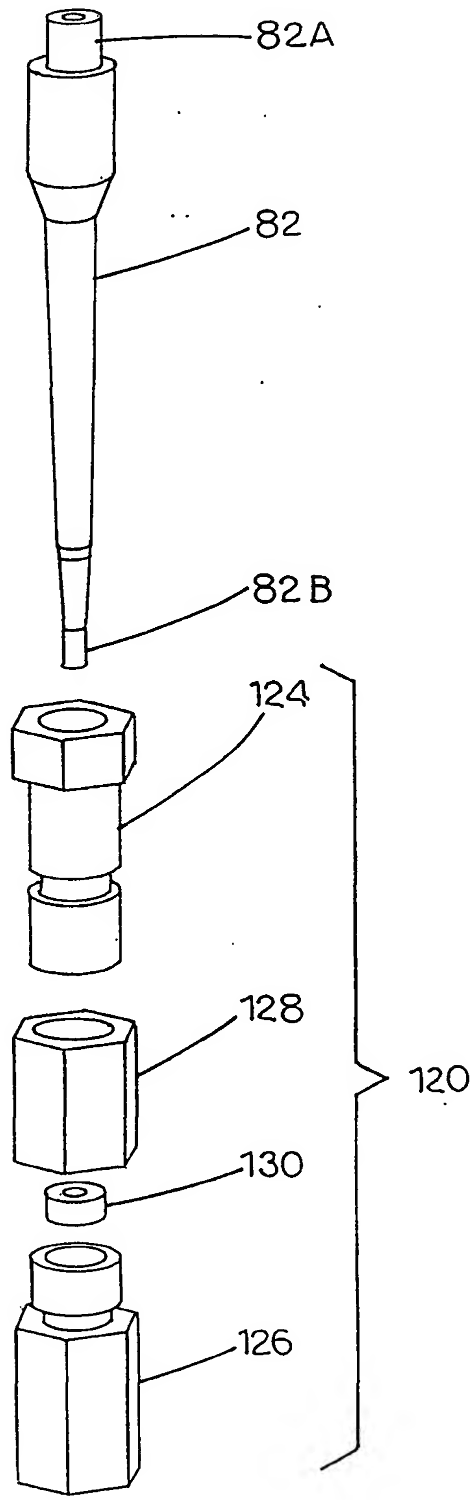

Fig.8

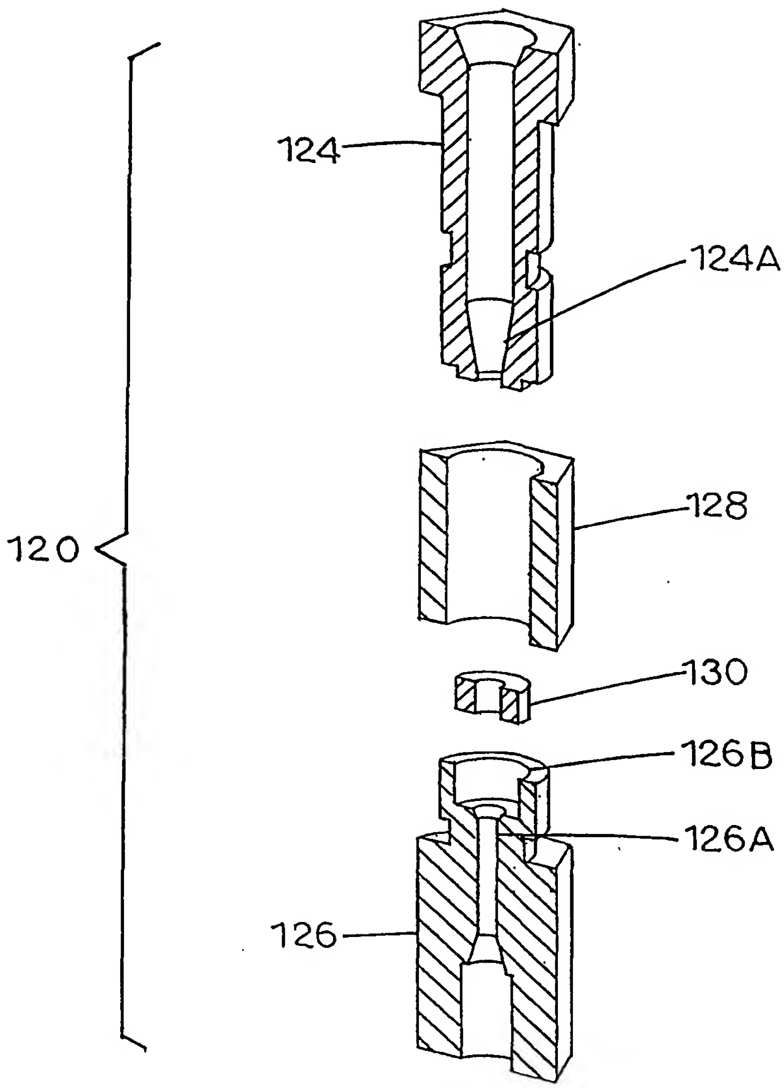

Fig. 9

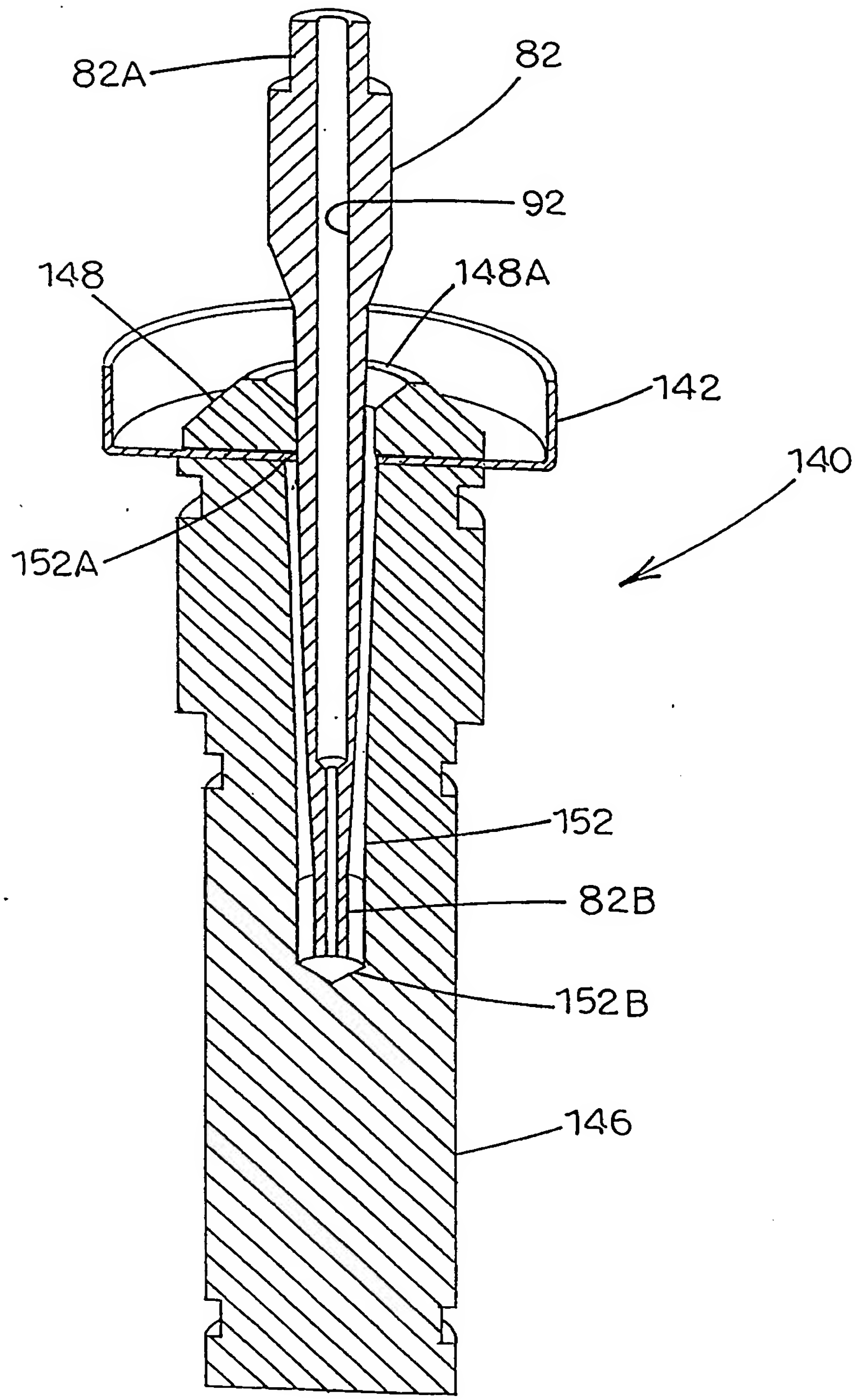

Fig.10

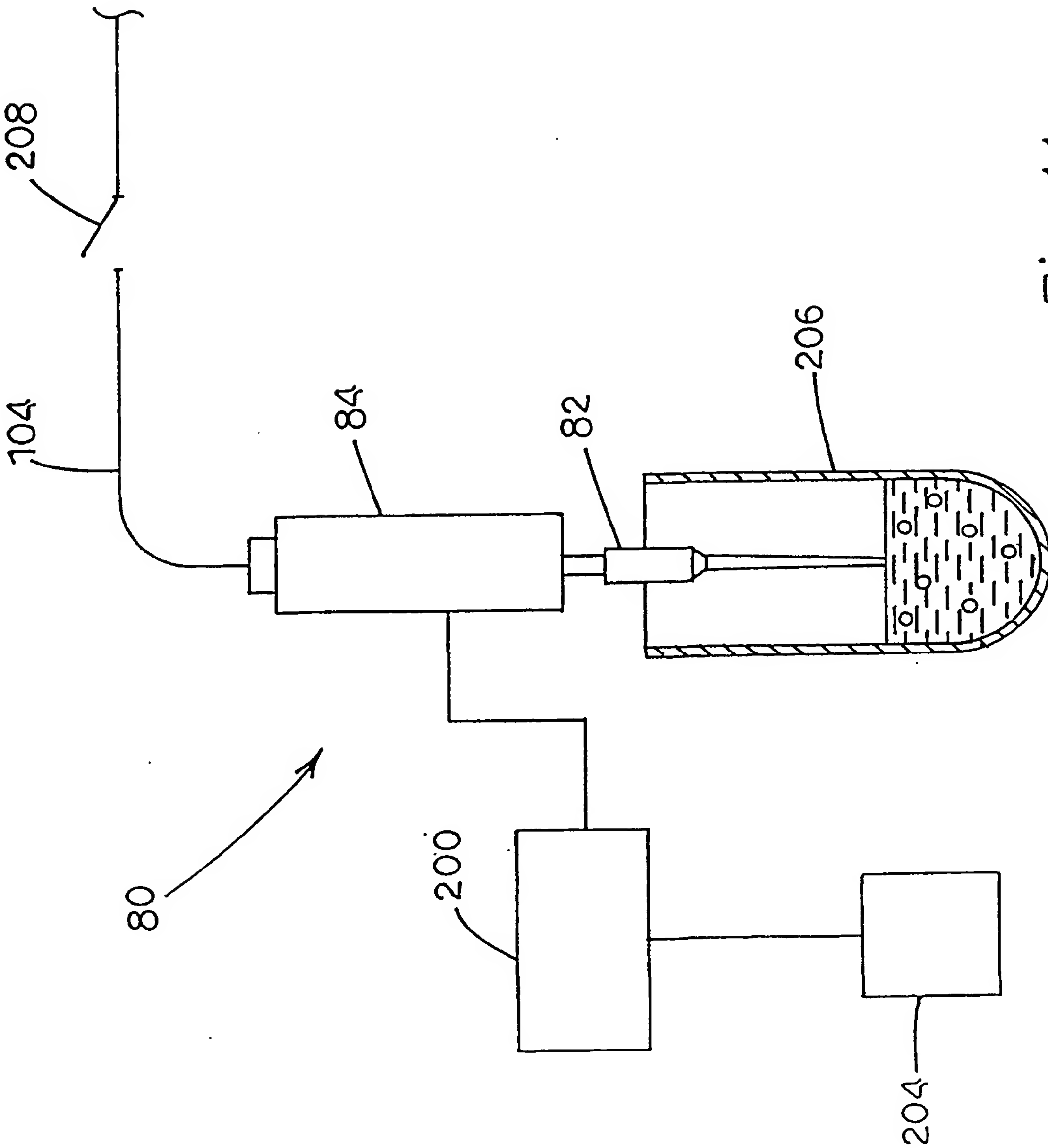

FIG.11

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(74) Agents: **LEVY, David, J.** et al.; GlaxoSmithKline, Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709 (US).

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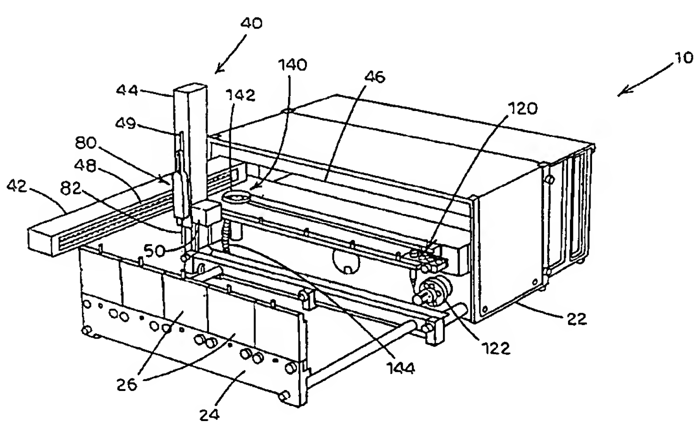
[Continued on next page]

(54) Title: ULTRASONIC TRANSDUCING PROBE WITH LIQUID FLOW-THROUGH CAPABILITY AND RELATED AUTOMATED WORKSTATION AND METHODS OF USING SAME



(57) Abstract: A hollow probe cooperates with an ultrasonic transducing device designed with liquid flow-through capability. The probe and transducing device are combined into a probe assembly, which can be integrated into an automated liquid handling workstation. As a functional component of the workstation, the probe can be connected to and manipulated by a robotic arm of the workstation, and thus programmed to move in three-dimensional space to and from various locations of the sampling apparatus. In particular, the probe can be inserted into the individual wells or test tubes of a plate or rack utilized to contain sample substances. The probe can be used to conduct a variety of liquid handling tasks and additionally can be used to ultrasonically excite sample substances contained in the individual wells of the plate, thereby improving dilution of such sample substances and increasing throughput of any given sample preparation procedure. A liquid level detection device can be connected to the probe assembly.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/44451

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01F11/02 G01N35/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01F G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, COMPENDEX, EMBASE, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 13, 30 November 1999 (1999-11-30) -& JP 11 230970 A (HITACHI LTD), 27 August 1999 (1999-08-27)	1,29
Y	abstract; figures 1-4	2-21
A		22-28, 30,31

X	US 5 026 167 A (BERLINER III SAMUEL) 25 June 1991 (1991-06-25)	29
Y	abstract; figures 1-5	1-20
A	column 3, line 62 -column 6, line 63	21-28, 30,31

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2003	30.05.03

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/44451

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 32038 A (FIBRASONICS INC) 1 July 1999 (1999-07-01)	29,31
Y	abstract; figures 1-6	1,3-10, 13,15-20
A	page 12, line 1 -page 14, line 2	21-28,30
X	US 4 930 898 A (MILLER-IHLI NANCY J) 5 June 1990 (1990-06-05)	29
Y	abstract; figure 2	1-21
A		22-28, 30,31
T	"Misonix_Sonicator_Brochure (pdf download)" MISONIX, NY 11735, US, 'Online! 13 March 2003 (2003-03-13), XP002234571 Retrieved from the Internet: <URL:http://www.misonix.com/Products/index.cfm?fuseaction=viewproduct&prod=44&div=11&cat=21> 'retrieved on 2003-03-13!	1-10, 13-31
Y	EP 0 801 309 A (SANYO ELECTRIC CO) 15 October 1997 (1997-10-15) abstract; figures 13-17 column 18, line 3 -column 19, line 52	11,12
Y	column 10, line 27 - line 52; figure 1	2,14
Y	US 5 365 783 A (ZWEIFEL RONALD A) 22 November 1994 (1994-11-22) abstract; figure 1 column 1, line 7 -column 5, line 2	11,12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

International Application No.
PCT/US 01/44451

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10,13-31

   Fluid handling workstation with integrated ultrasonic transducing probe with flow-through capability (claims 1-10 and 13-20) and process for preparing samples (claims 21-31) using the above system.

2. Claims: 11-12

   apparatus with ultrasonic transducing probe with flow-through capability and liquid level detection device.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/44451

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